Paraneoplastic syndromes and Autoimmune Encephalopathies

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Paraneoplastic Disorders vs. Autoimmune Synaptic Encephalopathies

- Paraneoplastic disorders
  - Antibodies targeted to intracellular antigens
  - Older, often with cancer (small or undetectable)
  - T-cell mechanisms
  - Resistant to treatment
- Autoimmune synaptic encephalitis
  - Extracellular targets
  - Younger, often without cancer
  - Antibody mediated
  - Responsive to treatment

Case 1

- 76 year-old woman
- 11/3/11: sudden onset vertigo, vertical diplopia on right gaze
- 11/7: slurred speech, imbalance, falling
- Exam: torsional nystagmus on lateral gaze, right worse than left; dysmetria FNF and HKS, severe gait ataxia
- Discharged with diagnosis of vestibular neuronitis and sinusitis

Case 1: Noncontrast MRI 11/3/11

Contrast MRI 11/16/11

Case 1: Re-evaluation 12/21/11

- Severe disability
- Unable to get out of bed alone
- Needed assistance to walk
Positive Anti-Yo Ab

Quest Diagnostics
Yo Ab, IFA, Serum: POSITIVE, 1:320 H
Mayo Lab
Purkinje cell cytoplasmic autoantibody Type 1 (PCA-1) positive, 1:30720 titer

Question 1: Diagnostic choices
1. Chest X-ray
2. Pelvic ultrasound
3. Mammogram
4. CT chest, abdomen and pelvis

CT 12/22/11: left periaortic nodes

Question 2: Diagnostic choices
1. CSF examination
2. Exploratory laparotomy and node removal
3. CT guided fine needle aspiration biopsy of nodes
4. Body PET-CT

CT guided retroperitoneal FNA
12/27/11: nondiagnostic

- INTERPRETATION
- FINAL DIAGNOSIS:
  - LYMPH NODE, RETROPERITONEAL, NEEDLE BIOPSY:
    - MINUTE FRAGMENTS OF SKELETAL MUSCLE, FIBROADIPOSE TISSUE AND LYMPHOID TISSUE (SEE NOTE)
- IMMUNOLOGIC CHARACTERIZATION BY FLOW CYTOMETRY:
  - NO SURFACE LIGHT CHAIN RESTRICTION BY B LYMPHOID CELLS DETECTED
  - CD4/CD8 T-CELL RATIO OF 2.1

NOTE: No definite evidence of malignancy is present in a limited sample. If clinical suspicion for lymphoma persists, re-biopsy is recommended.

Body PET-CT 1/20/12: mild left periaortic FDG activity
**Question 3: Diagnostic choices**

1. Complete serum paraneoplastic evaluation
2. Follow conservatively for development of tumor
3. Repeat FNA
4. TAH/BSO with exploratory laparotomy

**Microfocus of adenocarcinoma, left fallopian tube 2/1/12**

- A. **LEFT AORTIC LYMPH NODES, RESECTION:** NO TUMOR IDENTIFIED IN ONE LYMPH NODE (0/1)
- B. **UTERUS, CERVIX, BILATERAL TUBES AND OVARIAS, TOTAL ABDOMINAL HYSTERECTOMY WITH BILATERAL SALPINGO‐OPHORECTOMY:**
  1. **HISTOLOGIC TYPE:** SEROUS CARCINOMA IN LEFT FALLOPIAN TUBE
  2. **HISTOLOGIC GRADE:** WELL TO MODERATELY DIFFERENTIATED
  3. **TUMOR SIZE:** MEASURING 1.0 MM LIMITED TO LEFT FALLOPIAN TUBE
  4. **NO LYMPHOVASCULAR SPACE INVASION IDENTIFIED**
  5. **HAMARTIUMS:** ACT AND IMMUNOSTAIN SHOWS POSITIVE SPANNING IN THE TWO IMMUNE‐RELATED PATHOLOGIC FEATURES IS PARTIALLY LOST ON IMMUNOSTAIN SLIDES
  6. **LEFT OVARIAS SHOWING STROMAL HYPERPLASIA**
  7. **CHRONIC CERVICITIS, MILD INACTIVE ENDOMETRIUM**
  8. **LEIOMYOMA**
  9. **ADENOMYOSIS**

**Question 4: Management choices**

1. High dose steroids
2. Intravenous immunoglobulin
3. Plasma exchange
4. Rituximab and cyclophosphamide
5. No other therapy is available

**IVIG, carboplatin**

- 1/28/12 IVIG 0.5 g/k/d for 5 d then weekly X 3
- 3/12/12 carboplatin X 2; stopped
- No clinical benefit

**Classic Paraneoplastic Disorders—CNS**

- Encephalomyelitis
- Limbic encephalitis
- Cerebellar degeneration
- Opsoclonus myoclonus

**Nonclassic Paraneoplastic Disorders—CNS**

- Brainstem encephalitis
- Stiff person syndrome
- Necrotizing myelopathy
- Motor neuron disease
Classic Paraneoplastic Disorders--PNS
- Subacute sensory neuronopathy
- Gastrointestinal pseudo-obstruction
- Dermatomyositis
- Lambert-Eaton myasthenic syndrome

Nonclassic Paraneoplastic Disorders--PNS
- GBS, plexitis
- Subacute sensorimotor polyneuropathy
- Plasma cell dyscrasia with polyneuropathy
- Peripheral nerve and muscle vasculitis
- Autonomic neuropathy
- Myasthenia gravis
- Neuromyotonia

Paraneoplastic antibodies—six well characterized
- Yo (PCA-1)
- Hu (ANNA-1)
- Ri (ANNA-2)
- Ma2
- CV2/CRMPS
- Amphiphysin

Paraneoplastic cerebellar degeneration (Brain, 1951)

PCD (Brain, 1951): shrinkage of Purkinje cells

PCD Clinical Features
- Vertigo, oscillopsia, ataxia
- Rapid onset, progresses over days to weeks
- Nystagmus, especially downward beating
- MRI normal, rare enhancement
- Tumors: lung, ovary, breast, and lymphoma
- Coexisting LEMS
- 30% antibody negative
Question 5: Treatment choices

1. High dose steroids
2. Plasma exchange
3. Rituximab
4. Rituximab plus cyclophosphamide
5. No specific treatment

Case 1, MRI 10/17/12

Other Paraneoplastic Syndromes

Paraneoplastic encephalomyelitis (PEM)
- Affects widespread areas of CNS, DRG’s, and autonomic nerves
- Hippocampus, cerebellar, brainstem, dorsal root ganglia, spinal cord, autonomic ganglia and nerves
- Rapid onset over weeks to months
- Inflammatory CSF with OCB
- Antibodies correlate with some cancers

PEM Antibodies
- Hu (ANNA1)—PEM, sensory neuronopathy
  - SCLC, neuroendocrine
- CV2/CRMP—chorea, uveitis, optic neuritis
  - SCLC, thymoma
- Ri (ANNA2)—brainstem, opsoclonus
  - SCLC, breast, gynecological
- Ma2—limbic, diencephalic, brainstem
  - Testicular, lung, breast
- Amphiphysin—SPS, PEM, limbic
  - SCLC, breast

PEM Management
- Treatment of tumor
  - Surgery, chemotherapy, radiation therapy
- Immunosuppression
  - Steroids, IVIG, cyclophosphamide
- Prompt therapy essential
**Limbic encephalitis**
- Acute onset of short term memory loss, confusion, psychiatric symptoms
- Medial temporal FLAIR abnormalities
- EEG can show NCSE
- Anti-Hu, Ma2, CV2/CRMP5
- Can improve dramatically with prompt treatment of tumor and immunosuppression

**Opsoclonus-myoclonus**
- Back to back saccades
- Trunkal myoclonus, ataxia
- MR normal; CSF normal or inflammatory
- Disinhibition of fastigial nucleus
- Most no known antibody
- Adult: gyn, breast, SCLC; rarely with anti-Ri
- Child: neuroblastoma (new or recurrent)
- Children respond better to immunosuppression

**Anti-Ri Index Case**

**Stiff Person Syndrome**
- Nonparaneoplastic form
  - Anti-GAD Ab
  - DM, endocrinopathy
- Paraneoplastic form
  - Amphiphysin antibody
  - Breast, lung, lymphoma

**Autoimmune Synaptic Encephalopathies**
- Antibodies directed against extracellular neuronal or cell membrane proteins
- Characteristic syndromes
- Reversible
- Immune mediated
- Usually responsive to therapy

**Case 2**
- 45 year-old man
- 4/22/12: sudden short term memory loss and perseveration
- 4/23/12: Evaluated by Kaiser neurology; vitamin B12 195; treated with B12; no benefit
- 5/27/12: GTCS in sleep
  - Outside ED: AF with RVR, Na 127; cardioverted, Rx Keppra
- Transferred to Kaiser hospital
Case 2: MR 4/23/12: hyperintense medial temporal lobes

Case 2: Inflammatory CSF
- WBC 20 (90% M); RBC 450, protein 39, glucose 88
- HSV and VZV PCR negative
- Oligoclonal bands: positive (2)
- IgG synthesis indices normal

Question 6: Diagnostic choices
1. Anti-Hu
2. Anti-Ma2
3. Anti-amphiphysin antibody
4. Anti-voltage gated potassium channel antibody
5. Anti-glycyine receptor antibody

Antibodies are actually binding to other proteins complexed with VGKC
- LG1 (77%)
  - Leucine-rich glioma inactivated 1 (most important)
  - Highly expressed in hippocampus and neocortex
  - Mutations associated with autosomal dominant lateral temporal lobe epilepsy
- CASPR2 (11%)
  - Contactin associated protein-like 2
  - Cell adhesion molecule localizing VGKC's
- Contactin-2
  - Interacts with CASPR2 linking axon and glial membranes
- Other undefined antigens

Case 2: Voltage gated potassium channel antibody positive
- Athena: VGKC antibody 962 pmol/L (6/6/12)
- Mayo: Neuronal VGKC antibody identified (6/6/12)

Limbic encephalitis with VGKC antibodies
- Anti-LG1 limbic encephalitis
  - Classic limbic encephalitis (clinical, MRI)
  - CSF normal or mildly inflammatory
  - Fasciobrachial dystonic seizures
  - Hyponatremia—important early clue
  - Less than 20% neoplasm; most thymoma
- Anti-CASPR2 encephalitis
  - CNS dysfunction with neuromyotonia, allodynia, autonomic symptoms (Morvan syndrome)
Brain magnetic resonance images of a patient with immunotherapy-responsive voltage-gated potassium channel (VGKC) autoimmunity and renal oncocytoma illustrate increased signal in the left anterior cingulate gyrus and insular cortex on diffusion-weighted imaging (A, arrows) and fluid-attenuated inversion recovery sequences (B and C, arrows). Indirect immunofluorescence testing of the patient's serum revealed IgG binding to VGKC-rich synapses in mouse cerebellar cortex (D). ML indicates molecular layer; GL, granular layer; and PC, Purkinje cells (unstained).

Figure Legend:

Case 2: Workup

- Body CT 6/9/12 1.6 cm left adrenal solid mass with imaging c/w myolipoma; right lower pole exophytic renal mass with imaging c/w cyst
- Body PET-CT 6/21/12 negative
- Paraneoplastic antibody panel otherwise negative

Question 7: Treatment choices

1. Steroids alone
2. IVIG alone
3. Steroids + IVIG
4. Steroids + plasma exchange
5. Left adrenalectomy

Case 2: Treatment

- Solumedrol 1 gram then 250 mg qid started 6/10/12; prednisone 60 mg qd
- IVIG 0.4 g/kg/d for 5 d started 6/16/12
- Plasma exchanges started 7/3/12
- Marked improvement by 9/27/12

Case 3

- 23 year-old woman
- 9/14/09: sudden confusion, poor memory and attention, insomnia, anorexia, dysarthria. Progressed to agitation, stupor, incontinence, oral dyskinesias, rhythmic tonic clonic movements over next 2 weeks
- 10-15 min episodes of sinus tachycardia, and HTN
- Fevers without leukocytosis
Case 3: CSF

- CSF 9/20/09
  - W 59, (90% M), R 0 prot 23, gluc 59
  - OCB not done
- CSF 10/10/09
  - W 42 (100% M), R 0, prot 13, gluc 76
  - OCB 3
- CSF and blood encephalitis serologies all negative; CSF HSV and VZV PCR negative
- Serum rheumatic and vasculitis labs negative
- Anti-Hu and anti-Yo negative

Case 3: Body CT 9/25/09
Solid 5 cm mass in tail of pancreas

Case 3: MR 9/20/12

Question 8: Diagnostic choices
1. Body CT
2. Pelvic ultrasound
3. Urine catecholamines
4. Chest X-ray

Question 9: Diagnostic tests
1. Anti-NMDA receptor
2. Anti-AMPA receptor
3. Anti-GABA B receptor
4. Anti-Gly (alpha-1 subunit) receptor

Case 3: Serum and CSF positive for anti-NMDA receptor antibodies
- Antibodies against the NR1 subunit of NMDA receptor
- Lead to rapid and reversible loss of surface NMDAR
- Symptoms and course mimic dose dependent effects of PCP and ketamine
- Symptoms correlate with serum and CSF titers
- May result in selective inactivation of GABAergic neurons
Anti-NMDAR Encephalitis

- Common: 4% of patients with encephalitis
- Second most common cause of immune mediated encephalitis, after ADEM
- Young women and children
- Viral prodrome, then initial phase within 2 weeks, severe psychiatric symptoms and memory loss
- Second phase with stupor, dyskinesias, autonomic instability, hypoventilation
- CSF lymphocytic pleocytosis, OCB (60%)
- MR nonspecific hyperintensities on FLAIR

Tumor and anti-NMDAR encephalitis

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Anti-NMDAR encephalitis epidemiology

- 80% women; 55% of women >18 y/o have tumor (ovarian teratoma)
- Only 5% of men have tumor (testicular germ cell)
- Black women have ovarian teratomas more frequently

Question 10: treatment choices

1. Needle biopsy of pancreas
2. Pancreatic tumor resection, steroids, IVIG
3. High dose steroids plus IVIG
4. Rituximab plus cyclophosphamide
5. TAH/BSO

Case 3: Distal pancreatectomy, pseudopapillary neoplasm of pancreas

- Described by Franz in 1959
- 10:1 F:M predominance
- Low malignant potential; locally invasive
- Cure >95% when tumor confined to pancreas

Case 3: Tumor Reactivity with NMDAR
Case 3: treatment and outcome

- IVIG
- High dose steroids
- Postoperative hypoventilation requiring intubation for 1 week
- Slow recovery with intensive rehabilitation over 3 months
- Evaluated 12/21/09: normal and back to work

Anti-NMDA encephalitis: treatment and outcome

NMDAR Treatment Algorithm

Other Autoimmune Synaptic Encephalopathies

Anti-AMPA Receptor Encephalitis

- Middle aged women
- Limbic encephalitis
- Psychiatric symptoms, seizures
- Other autoantibodies (TPO, ANA, N-type Ca channel)
- 70% with tumor (lung, thymus, breast)

Anti-GABA B Receptor Encephalitis

- Limbic encephalitis, seizures
- SCLC or neuroendocrine tumor of lung
- Other autoantibodies
Antibody to Glycine Receptor Encephalitis

- Progressive encephalomyelitis with rigidity and myoclonus
- Similar to stiff-person syndrome
- Sleep and behavioral disturbances
- Seizure
- Pruritus

Paraneoplastic Autoantibody Evaluation (Mayo Lab, #83380)

- ANNA-1 (anti-Hu; sensory neuropathy, PEM, SCLC and other neuroendocrine CA)
- ANNA-2 (anti-Ri; brainstem encephalitis, opsoclonus; SCLC, breast and gyn CA)
- ANNA-3 (anti-neuronal nuclear Ab; Purkinje cell nuclei; multifocal deficits; lung CA)
- AGNA-1 (anti-glial nuclear Ab; Bergmann glia of Purkinje cell layer; small cell lung CA, LAKs)
- PCA-1 (anti-Yo; targets Purkinje cell cytoplasmic protein CDR2; breast and gyn CA, Hodgkin’s)
- PCA-2 (cytoplasmic neuronal staining; multifocal deficits, small cell lung CA)
- PCA-3 (dendritic spine of Purkinje cells; cerebellar degeneration; Hodgkin’s disease)
- Amphiphysin Ab (postsynaptic surface of synaptic vesicles; SPS and PEM, SCLC, breast CA)
- CRMP-5-IgG (anti-CV2 targets CRMP5 protein; PEM, SCLC, thymoma)
- Striated muscle Ab (target contractile elements; weakness; RA on penicillamine, thymoma)
- P/Q-type Calcium Channel Ab (presynaptic NMJ channels; LEMS; paraneoplastic cerebellar ataxia, encephalomyeloneuropathies, and autonomic neuropathies)
- N-Type Calcium Channel Ab (postsynaptic NMJ channels; LEMS and other disorders; SLLC and others)
- AchReceptor Binding Ab (MG)
- AchGanglionic Neuronal Ab (nicotinic ganglionic receptor; autoimmune dysautonomia, adenocarcinomas and other cancers)
- Neuronal (V-G) K+ Channel (several antigens; limbic encephalitis, Mowani’s, thymoma)
- Reflex tests: GAD65 Ab; Ach receptor modulating Ab; NMO-IgG

Mayo Lab Paraneoplastic Evaluation Algorithm

NMDA Receptor (NR1) Antibody: Athena Diagnostics #419

PERM (Fogan, 1996)—anti-Glycine Receptor antibody?